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Left-handed topology of super-secondary structure formed by aligned α-helix and β-hairpin

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A novel super-secondary structure common for many non-homological proteins is considered. This folding pattern, consisting of adjacent along the chain α-helix and β-hairpin, has an aligned packing. It is found that one of the two possible 'mirror-symmetrical' topologies is observed in proteins. The α-helix + β-hairpin structures have a similar pattern of hydrophobic residues in their amino acid sequences. The remaining part of a molecule or a domain is almost always located on the same side of the considered folding pattern. These results can be used in the prediction of three-dimensional protein structure and protein design.

α-Helix; β-Hairpin; Super-secondary structure; Amino acid sequence; Prediction

1. INTRODUCTION

Three-dimensional structures of proteins are very complicated and irregular. Nevertheless, proteins often have similar or even identical folding patterns even if they are quite different from both functional and philogenetical points of view [1–6]. These folding patterns consist of secondary structure segments (α-helices and/or β-strands) and are also called super-secondary structures. Super-secondary structures are of particular value in protein prediction and design since they have the most pronounced relationship between amino acid sequences and three-dimensional structures.

In this paper a new super-secondary structure formed by an α-helix and a β-hairpin is considered. The relationship between its structure and amino acid sequence is also discussed.

2. DESCRIPTION OF THE α-HELIX + β-HAIRPIN STRUCTURE

Inspection of protein structures shows that many of them (for example [7–20]) have a similar folding pattern formed by an α-helix and a β-hairpin. These super-secondary structures have the following common features: (i) the α-helix and the β-hairpin have an aligned arrangement (the dihedral angle Ω between the α-helical axis and that of the β-hairpin is from 0° to −30°); (ii) the crossover between the α-helix and the β-hairpin has 2–7 residues if counted from the first residue with a non-helical conformation to the last residue which does not form a β-structural H-bond; (iii) the interior of these structures (at least in the region near the crossover) consists of tightly packed side chains belonging on the one hand to the α-helix, and on the other to both β-strands.

In principle, two mirror structures of such an α-helix + β-hairpin folding pattern could be imagined (Fig. 1). One of the most significant results of our analysis is that, in proteins, the β-strands of the hairpin, together with the connected α-helix, form a turn of a *left* superhelix (Fig. 1a). This rule is true irrespective of the direction (in terms of N-, C-ends) of the chain within the structure.

We have found this folding pattern in more than 30 proteins. To describe the general situation as concerns the α-helix + β-hairpin structures in proteins, we should mention that this type of structures is the most widespread (≈65%). The remaining structures (≈35%) consist of an α-helix and a β-hairpin with orthogonal (Ω=±70°) rather than aligned packing (e.g. [21]) or an α-helix and a β-hairpin which virtually have no contacts (e.g. [22]). They have both the left-handed and the right-handed topology. A few right-handed aligned α-helix + β-hairpin structures were also found. However, in this case only one β-strand contacts the α-helix in the region near the crossover, while the second one interacts with other parts of the structure (e.g. [23]).

3. RELATIONSHIP BETWEEN AMINO ACID SEQUENCES AND THE α-HELIX + β-HAIRPIN STRUCTURES

Analysis of known α-helix + β-hairpin structures has shown that the most conservative part of their three-dimensional arrangement is placed near the crossover, where the two β-strands and the α-helix are tightly packed. As a rule, a residue side chain buried in the interior of a molecule is hydrophobic [24,25]. In accordance with this principle we might expect that side chains formed a close packing interior of the conservative part of the structure (residues a2, a2′, a1, b1, b2, c2 and c1 in Fig. 2) are hydrophobic. Our comparative analysis of the amino acid sequences coding for the α-helix + β-hairpin structures corroborate this suggestion. The 'internal' residues are hydrophobic in most of the struc-

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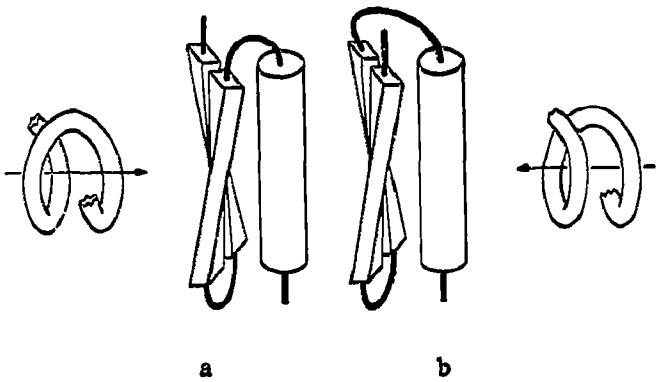

Fig. 1. (a) Left-handed and (b) right-handed topology of the α-helix + β-hairpin structure.

tures, irrespective of whether or not the structures are taken from homologous proteins (Fig. 3). It is worthwhile to note that the α-helix + β-hairpin structures have two possible arrangements of the elements of the secondary structure along the chain; α-helix–β-strand–β-strand (αββ) and β-strand–β-strand–α-helix (ββα). Alignment of the sequences coding for the ββα-structure and its stick and ball representation in space are shown in Fig. 3a and Fig. 2. The αββ-structure has another distribution of the 'internal' residues a3, a2, .. c1 shown in Fig. 3b.

As concerns the other parts of the structure, i.e. the hairpin loop and the helix-hairpin crossover, they are more variable in length and diverse in sequence.

4. ARRANGEMENT OF THE α-HELIX + β-HAIRPIN STRUCTURE RELATIVE TO THE OTHER PART OF PROTEIN STRUCTURE

The α-helix + β-hairpin structures were found mostly

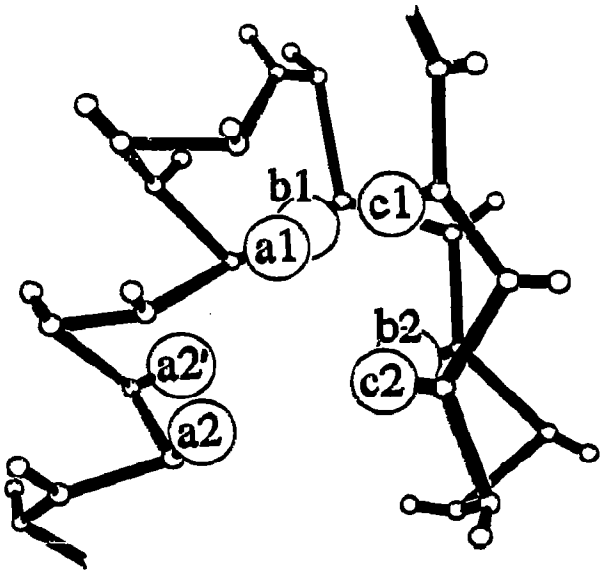

Fig. 2. Stick and ball representation of the ovomucoid ββα-structure [15]. Enlarged spheres denote 'internal' residues.

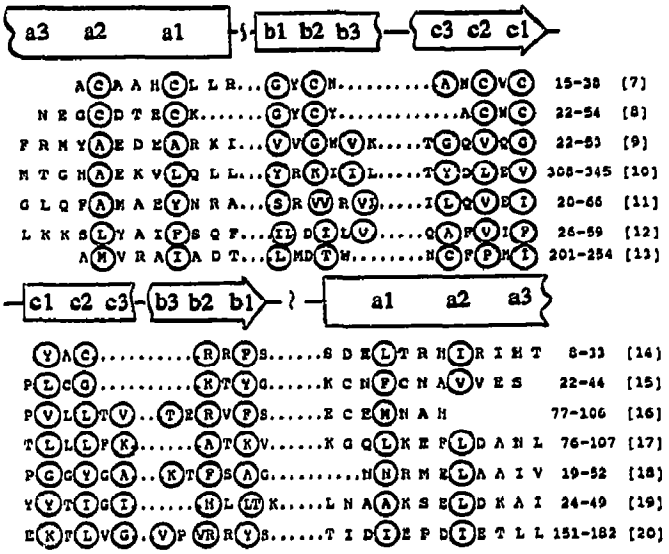

Fig. 3. Alignment of the typical amino acid sequence coding for the αββ- and the ββα-structure. Structurally similar 'internal' residues are encircled. References indicate sapecin [7], scorpion neurotoxin [8], acylphosphatase [9], seryl-tRNA-synthetase [10], cystatin [11], U1 A protein [12], creatin amidinohydrolase [13], Zif268 zinc-finger domain [14], ovomucoid [15], bacterial protein proteinase inhibitor [16], thioredoxin [17], RNAse H [18], T4 lysozyme [19], glutathione peroxidase [20].

in the small- and medium-sized (35–200 residues) α/β domains and proteins [7–20]. The smallest among them are zinc-finger domains [14] and sapecin [7] which have only the ββα-structure and the αββ-structure, respectively. Analysis of the other α/β proteins shows that the more linearly distant from the α-helix β-strand of the considered super-secondary structure always interacts with an antiparallel β-strand of the remaining part of the structure (Fig. 4), while the β-strand, adjacent to the α-helix, as a rule, does not interact with a polypeptide chain. There is an exception in some cases [9,20] where the adjacent β-strand forms 1–2 hydrogen bonds with

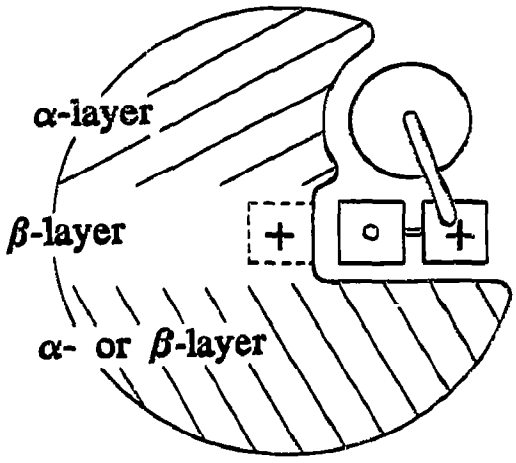

Fig. 4. Schematic representation of typical arrangement of the α-helix + β-hairpin structure in proteins.

the short fragment of the chain. Thus, the side of the distant β-strand almost always faces the remaining part of the protein structure, while the other side faces water (Fig. 4).

5. DISCUSSION

The reasons for the observed features of the α-helix + β-hairpin fold will be the subject of our further consideration. However, even now we could conclude that the 3D arrangement of the α-helix and the β-strands near the crossover is similar to the same region of the Rossmann fold [1]. The handedness of the Rossmann fold has been explained by the intrinsic twist of β-structures [2,26–28]. Because of this twist the right-handed connection in the Rossmann fold, as well as the left-handed one in our fold (Fig. 1a), uses the 'shortest' and less 'stretched' way than the alternative variants (Fig. 1b). So by analogy with the Rossmann fold, the handedness of the α-helix + β-hairpin fold might be explained by the twist of β-structures and as a consequence by optimum helix–hairpin connection.

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